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Vaccine therapy for HIV: A historical review of the treatment of infectious diseases by active specific immunization with microbe-derived antigens

Donald S. Burke

A review of the history of 'vaccine therapy' for infectious diseases is presented. The concept originated when Auzias-Turenne introduced 'syphilitic vaccination' or 'syphilization' as a treatment for syphilis in Paris in the mid-1800s; his clinical studies probably influenced Pasteur's successful rabies postexposure vaccine trials. Robert Koch in Berlin in the 1890s observed that inoculation of tuberculin into patients with tuberculosis induced an inflammatory response in affected tissues, and advocated 'tuberculin therapy'. Sir Almroth Wright in London in the early 20th century devised methods to measure changes in serum 'opsonizing' activity in response to therapeutic inoculations with microbe-derived vaccines. Since the advent of antibiotics, active specific immunization with microbe-derived antigens (vaccine therapy) has been largely forgotten as a strategy for treatment of infectious diseases. Advances in antigen production and in molecular immunology now permit new tactics to probe, analyse and selectively alter in vivo human immune responses to infectious microbes. Our recent demonstration that vaccine therapy can boost natural immunity to HIV in infected patients should rekindle interest in this approach.

Keywords: Vaccine therapy; vaccine; AIDS HIV; microbe-derived antigens

'There is at bottom only one genuinely scientific treatment for all diseases, and that is to stimulate the phagocytes. Stimulate the phagocytes. Drugs are a delusion.' (George Bernard Shaw in *The Doctor's Dilemma*, 1906).

It was recently reported that a genetically engineered glycoprotein antigen derived from the HIV *env* gene (gp160), when administered to HIV-infected patients by repeated parenteral inoculations, boosted both humoral and cellular immune responses to HIV[1,2]. Although this Phase I study did not prove efficacy of 'vaccine therapy' for HIV, it did establish that *in vivo* natural host immunity to HIV is responsive to physician-directed manipulations. One may hope that this strategy can be exploited to suppress viral replication and prolong patient survival. Phase II efficacy studies are currently under way.

Other research groups have recently tried similar approaches by administering other HIV-derived therapeutic products. Zagury and colleagues attempted to immunize patients with paraformaldehye-fixed autologous lymphocytes that expressed genetically cloned vaccinia-expressed HIV antigens on their surface[3-6]. Salk and co-workers inoculated patients with proprionolactone- and radiation-inactivated whole HIV virions[7,8]. Scolaro *et al.* superinfected asymptomatic late-stage patients by inoculating them with replication-competent HIV isolated from an asymptomatic patient who had had a long and benign course[9]. Vaccine therapy studies are also now under way by AIDS Clinical Trials Groups under the auspices of the National Institutes of Health. Common to all these studies is the hypothesis that the clinical course of HIV can be slowed or reversed by therapeutic products derived from HIV proteins.

These studies with HIV are only the most recent in a long history of efforts to treat infectious diseases by active specific immunization with microbe-derived antigens. Few physicians today, trained as they were during the antibiotic era, are aware of the role of vaccine therapy in the evolution of concepts in microbiology and immunology.

In contemporary medicine the term 'vaccine' is usually restricted to the context of 'pre-exposure' prophylaxis, where an antigen is administered to a healthy uninfected person who is at risk of exposure. 'Vaccines' are also sometimes administered promptly after known exposure to a pathogen, for 'postexposure prophylaxis'; this is commonly done for rabies and occasionally for other infections such as hepatitis B virus. *Figure 1* summarizes differences between the use of vaccines for prophylaxis, postexposure prophylaxis, prevention of recurrences and therapy. By today's conventions 'vaccine therapy' might seem an oxymoron, yet in the past the term was widely

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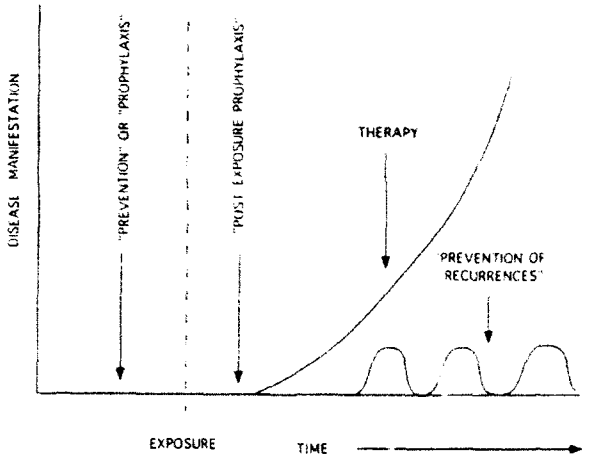

Figure 1 Schematic representation of possible uses of vaccines for altering the course of infectious diseases. Vaccines are administered before exposure to the microbe (vaccine for 'prevention' or for 'prophylaxis'); after exposure to the microbe but before clinically apparent disease ('postexposure prophylaxis'); or after infection with the microbe is already manifest ('vaccine therapy'). Vaccines can also be used to prevent reappearance of manifestations in recurrent diseases

used to convey 'active specific immune therapy with microbe-derived antigens'. Given its brevity, and especially given the established precedent for its use as presented in this paper, 'vaccine therapy' should be considered a legitimate, even preferred, term.

This paper is not intended to be a detailed review of the current work on HIV vaccine therapy. Instead, it is intended to examine the extensive historical precedents for this rather unorthodox strategy.

ADUMBRATIONS OF VACCINE THERAPY (1850–1885)

The success throughout Europe in the first decades of the 19th century of Jennerian 'vaccination' against smallpox prompted searches for vaccines against other diseases. In 1850 the quixotic French physician Auzias-Turenne proposed that inoculations with matter from soft chancres could be used as a therapy for syphilis[10,11]. Since soft chancres were associated with relatively mild, local disease, and hard chancres with chronic disabling disease, he hypothesized that the mild disease variant could interfere with, and protect against, the severe disease variant, much as occurred with vaccinia and variola. He immodestly wrote 'I am introducing a new concept into science,' explaining 'Consequently I must adopt a new term to express it: the term is 'syphilitic vaccination' or 'syphilization''[12,13]. Unaware of the different aetiologies of soft chancres (*Haemophilus ducrei*) and hard chancres (*Treponema pallidum*), Auzias-Turenne zealously advocated 'syphilization' to treat syphilitic prostitutes as a public health control measure[14]. There can be no doubt of the sincerity of his belief: he tried the experiment on himself[15]. Although Auzias-Turenne and syphilization did win medical disciples in other European countries[16–19], his ideas were largely rejected in France. In 1852 the Imperial Academy of Medicine judged that 'Neither reasoning, nor analogy, nor experiments on animals, nor observations of people who are said to be syphilized by natural means can justify the application of syphilization to either healthy persons or sick ones'[20]. The debate over the public health value of syphilization continued for decades, and dominated the 1st International Medical Congress in Paris in 1867[11,21,22]. Auzias-Turenne also claimed success with vaccines for other diseases, such as pleuropneumonia of cattle, using inoculations of 'virus taken from the lung' for both use in prophylaxis and in the therapy of this disease[23].

In retrospect, Auzias-Turenne's attempts at 'syphilization' were destined to fail for several reasons. Paramount were the impurity and antigenic irrelevance of his 'vaccines'. Nonetheless, Auzias-Turenne's theories probably had a lasting impact. His collected works were republished posthumously in 1878 in a volume entitled '*La Syphilization*', a copy of which was given to Louis Pasteur by his nephew Adrien Loir. According to Loir, Pasteur was intrigued, and often referred to the book as he began his studies on rabies[24,25].

Pasteur's celebrated success with postexposure prophylaxis of rabies in the case of Joseph Meister in 1885 is legendary. Not widely appreciated is just how quickly thereafter that Pasteur learned the limits of postexposure prophylaxis: in the Meister case the bite-to-vaccination lapse was 2 days. In the second case, also successful, of a teenage shepherd, the lapse was 6 days. However, in the third case, that of a 10-year-old girl bitten 37 days previously, Pasteur's postexposure vaccine failed to prevent rabies and death[26]. Subsequently the parents of one child who died following anti-rabies treatment brought a suit against Pasteur[27]. Pasteur never reported use of vaccine therapy in symptomatic rabies cases, possibly because of liability concerns, but more probably simply because he subscribed to the prevailing 'exhaustion theory' of immunity: that invading microbes failed to grow in an immune host because the prior infection depleted substances from the host that were critical to growth of the microbe[28].

KOCH AND VACCINE (TUBERCULIN) THERAPY FOR TUBERCULOSIS (1890–1911)

While Pasteur was lauded for his success with rabies vaccines in Paris, Robert Koch (a veteran of the Franco-Prussian War) in Berlin patiently laboured to derive practical applications from his 1882 proof that a mycobacterium is the cause of tuberculosis[29,30]. In an address to the International Medical Congress in August 1890 in Berlin, Koch droned on about the numerous substances he had tested for anti-tuberculous activity, all without success. Then, just before concluding, he dropped a bombshell[31]:

> In spite of these failures, I continued the quest and I ultimately found substances that halted the growth of tuberculosis bacilli not only in test tubes but in animal bodies . . . my study of these substances is not complete. I can only communicate that . . . in guinea pigs in which tuberculosis has already reached an advanced stage, the disease can be completely halted without otherwise harming the body.

Koch provided no information in this speech about the nature of the curative substance. Nonetheless, the impact was profound. One American reported that 'one could divine that a great tidal wave in science was imminent – and that it centered upon the discovery of

Koch'[32] and a *Lancet* editorial gushed about 'the verge of a revolution in therapeutics'[33].

Three months later in November 1890, Koch published his first paper on the cure for tuberculosis, but here again he did not reveal the nature or composition of the substance, referring to it only as a 'brownish clear liquid'[34]. He claimed remarkable successes in treatment of patients with the substance, but noted that reactions were often rather severe in tuberculosis patients. In contrast, healthy humans scarcely reacted (the diagnostic uses of the material were immediately apparent). Finally, under substantial pressure from the international medical community, Koch revealed that the new therapeutic substance was a solution or suspension of glycerin and extracts from tubercle bacillus cultures, a prototype of what has subsequently been called tuberculin[35,36]. Treatments were administered by subcutaneous injections of dilute fluid in the middle of the back between the scapulae.

Without an understanding of specific immunity or the immune system, Koch's hypothesis for the mechanism of action of tuberculin was that it somehow induced an unfavourable environment for bacillus growth[37]:

> The tubercle bacilli produce through their growth certain substances, which in the living element of their surroundings influence the cells in different manners, indeed negatively influence them ... the tubercle bacillus finds a rather undesirable nutritional basis.

Patients flocked from around the world to receive the tuberculin treatment in Berlin[38–40]. Lord Lister sent his niece, and Paul Ehrlich, Koch's assistant (who was destined for a Nobel prize of his own for his work on humoral immunity), was a patient. Arthur Conan Doyle, creator of Sherlock Holmes, returned to England to herald Koch's triumph[41].

Thousands of patients promptly received the new therapy. However, a compendium of 55 reports of clinical trials, written by giants of Prussian medicine (Virchow, Henoch, Jolly, Trendelenburg and others), published in early 1891 raised the first doubts: only 18 of the 1769 patients treated were considered cured, while 55 died[42]. Where lesions were visible, the treatments usually provoked a local inflammatory response. This was particularly pronounced in cases of lupus vulgaris, tuberculosis of the skin.

Because of the low cure rate, the severe systemic reactions and the excess mortality, enthusiasm for tuberculin vaccine therapy rapidly turned to disenchantment. Gibier in New York opined 'we are, for the moment, assisting at the spectacle of one of the greatest medical and scientific delusions that have ever existed'[43]. In May 1891, an editorial in the *Journal of the American Medical Association* summarized[44]:

> The therapeutic results obtained by tuberculin may be summarized in two statements: (1) ... the agent exerts a specific effect on all tubercular lesions, by starting an inflammatory process in and around the tubercular tissue, which tends to cure the disease. (2) This reparative change has not proceeded up to the actual cure in the majority of cases hitherto treated.

George Sternberg, the leading American microbiologist of the era, criticized Koch's studies and called for controlled clinical trials[45]:

> It is evident that in a disease in which recovery sometimes occurs independently of treatment, and ... in the absence of 'controls' such as we find it necessary to employ in experimenting upon the lower animals, the reported results ... must be accepted with great caution.

Although vaccine therapy for tuberculosis was substantially curtailed during the 1890s, Koch stubbornly (perhaps presciently) clung to his belief that tuberculin could have a salubrious effect. He continued to devise and experiment with new variations of tuberculin. Even in his Nobel Prize acceptance speech in 1905, Koch spoke of vaccine therapy with tuberculin 'in order to achieve swifter, and in particular, more lasting cures'[46].

In retrospect, Koch should be credited with precedence for having proved the feasibility of vaccine therapy. He produced a relatively pure and specific antigen preparation, and convincingly demonstrated that inoculation of this microbe-derived antigen regularly provoked a specific immune response around the sites of infection in tuberculous patients. Koch's tuberculin therapy was appropriately rejected as unsafe and lacking appreciable clinical benefit, and these studies are now usually cited only to credit Koch with the discovery of delayed-type hypersensitivity[47]. Nonetheless, in these reports Koch also established, for the first time, that a natural immune response could be boosted. Shortly thereafter Trudeau, among others, confirmed in animal models Koch's observations that 'tuberculin does not cure experimental tuberculosis in the guinea-pig, although its specific influence on the primary lesions is indisputable'[48].

ALMROTH WRIGHT AND THE GENERAL THEORY OF VACCINE THERAPY (1902–1947)

Almroth Wright's paper, published in 1902 and subtitled 'Generally on the treatment of localized bacterial invasions by the therapeutic inoculation of the corresponding bacterial vaccine' is the first unambiguous exposition of the theory behind vaccine therapy, explaining his own as well as Koch's observations that natural immunity to an infectious organism can be boosted[49]. He used a heat-inactivated vaccine derived from autologous cultures of pure *Staphylococcus aureus* to boost the 'agglutinating power exerted by the serum upon the staphylococcus' of a patient with recurrent furunculosis. He compared[49] his clinical experiment with that of Koch:

> Much that is of value can be learned upon this subject by a careful consideration of Koch's tuberculin inoculations and by a comparison of these with the inoculations of staphylococcus vaccine with which we have been dealing above. In each case a bacterial vaccine is, for therapeutic purposes, inoculated into patients already the subject of a corresponding infection. In each case, as the result of the inoculation, an acute inflammatory reaction is set up at the seat of infection. In each case, again as a result of the inflammatory reaction in question, the nidus in which the bacteria are lodged is broken up.

Shortly thereafter, he described substances in the serum which prepared the bacteria for the leucocytes to digest,

and from the Greek word for 'cooked food' dubbed these substances 'opsonins'[50–53]. Wright refined his theory so that the opsonic activity (index) of the serum served as a guide for vaccine therapy, and then predicted[54]:

> The time will come when ... an endeavour will be made in every case to arrest the invasion and to prevent its recurrence by calling into action the forces of resistance which lie latent in the organism. The physician of the future will, I foresee, take upon himself the role of an immunizator.

George Bernard Shaw, a friend of Wright's, became a convert and wrote *The Doctor's Dilemma*, a play about ethical problems encountered in vaccine therapy trials (a quotation from which introduces this article)[55].

In 1910 a lengthy debate on vaccine therapy ensued for six straight sessions at the Royal Society of Medicine. Wright opened the proceedings with an address entitled 'Vaccine therapy: its administration, value, and limitations'[56].

The doctrine of Vaccine Therapy flourished in Europe and the United States. One of Wright's contemporaries in a thoughtful 1905 review entitled 'The principles underlying the treatment of bacterial diseases by the inoculation of corresponding vaccines'[57] wrote:

> Whatever may be the final verdict as to the range of therapeutic inoculation, there is no doubt that, from a purely scientific side, the work of A.E. Wright has opened up new fields, and has proved itself heuristic in a high degree, and when the history of latter-day medicine comes to be written, it is probable that his work will rank beside the classical researches of Pasteur, Lister and Koch.

Eminent physicians wrote scholarly papers in respected journals on the theory and practice of vaccine therapy[58–63]. Indeed, beginning in 1911 and continuing to the present day, 'vaccine therapy' or 'vaccinotherapy' has been a standard Medical Subject Heading in the *Index Medicus*. The issues examined in these early publications were sometimes remarkably sophisticated. One author analysed the theoretical advantages and disadvantages of stock antigen vaccines versus autogenous antigen vaccines[64]. Another discussed aerosol delivery of antigen so as to directly target respiratory tract immunity[65].

Vaccines for therapy became standard items in the Pharmacopoeia, and textbooks with titles like *The Opsonic Method of Treatment: A Short Compendium for General Practitioners, Students, and Others* or *Vaccine Therapy in General Practice* became commonplace[66,67]. A new *Journal of Vaccine Therapy* appeared in 1912 which carried articles such as 'The principles of therapeutic immunisation as applied by the general practitioner', 'The vaccine treatment of typhoid fever', and 'The vaccine treatment of septicemia'[68–70].

Tuberculin therapy for tuberculosis enjoyed a parallel resurgence, and textbooks on *Tuberculin in Diagnosis and Treatment* and *Tuberculin and Vaccine in Tubercular Affections: A Practical Guide for the Utilization of the Immune Response in General Practice* were published[71,72]. In the 1916 (eighth) edition of his *Principles and Practice of Medicine*[73] Sir William Osler wrote:

> Of late years there has been a reaction in its [tuberculin therapy] favor, and now tuberculin is again lauded by some fanatics as the one and only means of cure in the disease. Unquestionably in suitable cases it has a very beneficial influence: the difficulty is to decide which they are. At present so indiscriminate is its use that an estimation of the results is very difficult.

Vaccines were customarily used as therapy for common chronic or recurrent bacterial diseases for which the organism could be isolated and grown *in vitro*, such as staphylococcal skin infections and chronic gonorrhoea[74–76]. Vaccine therapy was also advocated for life-threatening conditions such as endocarditis or bacterial meningitis where other therapeutic options were limited[76,77].

The zeal for vaccine therapy also led to its use for diseases in which bacteria were suspected but not proven to have a pathogenetic role, such as bronchial asthma or rheumatoid arthritis[78,79]. Other physicians believed that specific identifiable infections should be treated, but that vanishingly minute doses were effective[80]. Disciples of yet another minor off-shoot of vaccine therapy believed in 'Protein shock therapy', claiming that vaccines for treatment of infectious diseases need not be antigenically related to the infecting organism – that any foreign protein would do[81]. It is a measure of the appeal of vaccine therapy that it came to be applied even in situations where the vaccine antigens bore an unknown or even no relationship to the offending pathogen.

Survey data obtained from 1261 physicians during the mid-1920s in New York, Indiana and Michigan revealed that two-thirds had used bacterial vaccine therapy at least once, and that over one-third were actively using bacterial vaccine therapy in their own practice[82]. The disease most commonly treated with vaccines was furunculosis. Not surprisingly, most of those using vaccine therapy believed that they obtained good results. However, none considered the use of vaccines to be 'a superior general method of treatment of infectious diseases'. Eleven per cent reported having observed some harmful results.

A similar survey among 257 responding United States tuberculosis specialists revealed that 30% currently used or had actively used tuberculin therapy[82]. The majority of these physicians who employed tuberculin therapy believed that they in general obtained 'good' results. However, tuberculin vaccine therapy was considered to be potentially dangerous: collectively these physicians reported seven deaths attributable to tuberculin therapy, most of which were 'quiescent cases that have been lighted up immediately after injection'[82].

Thus, vaccine therapy was extensively used during the early years of the 20th century, but did it actually work? What evidence is there that vaccines were efficacious in the treatment of chronic infectious diseases? Most medical historians have rendered unfavourable assessments[83]. For example, one historian writes, 'It is doubtful if this form of treatment produced any good results and certainly in most cases, it was valueless to the point of fraudulence'[84]. This appraisal may be unduly harsh: the non-committal positions taken by Sternberg and Osler (noted above) were probably fairer: despite a huge literature of case reports and uncontrolled series, no adequately controlled clinical trials were published. This void is in part due to the fact that controlled clinical trials were uncommon in clinical medicine before the 1930s[85]. However, Wright's attitude that controlled

vaccine therapy trials were unethical also probably contributed to the lack of convincing data[86].

While vaccine therapy study might be dismissed as lacking clinical efficacy, it is not so easy to dismiss evidence that vaccines, when administered to patients with chronic infections, were immunogenic. That is, vaccine therapy measurably boosted the pre-existent natural immune response. As noted above, tuberculin therapy in patients with tuberculosis regularly increased the inflammation at the sites of active tubercular disease, suggesting an increase in delayed-type hypersensitivity to tuberculosis antigens[31,48,87]. Perhaps more persuasive are Wright's published graphs showing prompt rises in serum opsonizing antibody activity immediately following each therapeutic inoculation[49,88]. Here again, a lack of adequate controls confounds the analysis. Wright's methods for measuring opsonizing activity were criticized by the renowned biostatistician Karl Pearson who deplored his cavalier indifference to statistical tests of significance: Pearson concludes one paper[89] critical of Wright's data analysis with the exhortation 'Statistics on the table, please!'

Although neither efficacy nor immunogenicity were unequivocally proven during these early years, the vaccine therapy school did spawn some unusually talented scientists. Foremost among Wright's pupils was Sir Alexander Fleming, discoverer of penicillin, who in 1906 at the age of 25 joined Wright's laboratory. Fleming received all his bacteriological training from Wright, and was serving as the Hospital Assistant Director of Therapeutic Inoculation at the time of his important discoveries[90,91]. Proud as he was of Fleming's accomplishment (which eventually propelled chemotherapy and antibiotics to the scientific fore), Wright never wavered in his preference for vaccine therapy over chemotherapy[52,53].

Wright's death in 1947 and the near simultaneous proliferation of potent antibiotics such as chloramphenicol, the aminoglycosides and the penicillins signalled the end of the golden age of vaccine therapy.

VACCINE THERAPY IN THE ANTIBIOTIC ERA (1950–PRESENT)

After 1950 vaccine therapy receded to the scientific backwaters. Publications appeared sporadically in subspecialty journals and usually dealt with chronic or recurrent infectious diseases for which there were no safe and effective antibiotics, such as viral infections like herpes simplex[92–95] or condyloma acuminatum[96–99], and fungal infections[100–103]. Although often engaging in concept, results were unimpressive.

The past decade has witnessed a modest resurgence in interest in vaccine therapy as a strategy to treat chronic infectious diseases. Vaccine therapy for tuberculosis is enjoying yet another revival. Intradermal injections of one billion irradiation-killed *Mycobacterium vaccae* have recently been advocated as a cost-effective tuberculosis public health control measure particularly suitable to developing countries[104]. Limited field trial data suggest favourable clinical and immunological effects, but these studies are small and unconfirmed[105,106].

Most recent efforts have been focused on three distinct disorders which share some common clinical and pathogenetic features: leprosy, cutaneous leishmaniasis and herpes simplex. These three diseases are all chronic or recurrent infections with predominant skin manifestations; all are intracellular pathogens for which cell-mediated immunity is thought to be important; and all can show a broad range of *in vivo* expression, thought to reflect variability in host immunity.

Leprosy

In Venezuela in the mid-1970s, Convit and colleagues observed that patients with the lepromatous (diffuse, multibacillary) form of leprosy were unable to clear heat-killed *Mycobacterium leprae* bacilli that had been injected intradermally. However, when the inoculation contained a mixture of *M. leprae* with a live attenuated tubercle bacillus (BCG), the *M. leprae* were successfully cleared along with the other mycobacterium[107]. These observations led to clinical vaccine therapy trials in which mixtures of *M. leprae* and BCG were repeatedly inoculated into hundreds of afflicted patients[108,109]. While clinical effects have not been dramatic, increased antibody titres, increased delayed-type hypersensitivity skin-test reactions and increased *in vitro* lymphocyte proliferation responses to *M. leprae* antigens have been observed[110,111]. Intradermal injection of recombinant interleukin-2 can activate a local response to *M. leprae* bacilli[112]. The central immunological defect in lepromatous leprosy appears to be selective T-cell unresponsiveness to *M. leprae*; it has been reported that this unresponsiveness is due to specific active suppression[113–115].

Leishmaniasis

Leishmaniasis is an insect-borne protozoal disease endemic throughout the tropics. Convit pointed out striking similarities between the clinical and histopathological features of leprosy and cutaneous leishmaniasis, and suggested that the pathogenesis of the two diseases might also be similar[116]. Inspired by the successes noted above with leprosy, Convit and his colleagues conducted large, randomized controlled trials in which a vaccine consisting of live BCG plus killed leishmania promastigotes was compared with the standard chemotherapy of intramuscular meglumine antimonate or to BCG alone[117]. Reported clinical efficacy has been excellent: the vaccine therapy resulted in cure rates of greater than 90%, comparable to that of the chemotherapy, and substantially better than the 42% cure rate with BCG alone[118]. However, immunological studies on treated patients have detected neither an increased lymphocyte proliferative response nor an increased antibody response to leishmania antigens in vaccinated patients[119]. Other smaller clinical vaccine therapy trials using purified soluble leishmania antigen fractions have also reported favourable clinical results[120].

Herpes simplex

Several vaccine therapy trials for herpes simplex virus (HSV) employing crude vaccine preparations were conducted during the 1950s and 1960s. None showed clear clinical benefit, and none was particularly scientifically illuminating[92–95]. Interest intensified in 1987, however, when Stanberry and colleagues working with a guinea-pig model of genital herpes observed that prophylactic HSV vaccination not only prevented initial infection, but also reduced the frequency and duration

of recurrences[121]. Subsequent experiments clearly showed that the same or similar vaccines inoculated into already infected animals were also effective in reducing the frequency and severity of recurrences by as much as 75%[122,123]. Glycoprotein D was most effective, and molecularly cloned and expressed products were active[124]. Vaccination of already infected animals boosted both pre-existent antibody titres and pre-existent lymphocyte proliferative responses to the glycoprotein, but the adjuvant, the timing of inoculations, and the route and dose are all important determinants of immunogenicity and efficacy in this animal model[125-129]. Human vaccine therapy trials have recently begun.

In contrast to this relatively limited current research on vaccine therapy for infectious diseases, active specific immunotherapy for cancer with tumour antigens is being aggressively pursued in clinical trials (reviewed in Ref. 130). Studies are regularly reported in a contemporary oncological analogue of the *Journal of Vaccine Therapy* entitled *Cancer Immunology and Immunotherapy*, but results are usually inconclusive. Active specific immunotherapy studies for cancer are consistently hampered by a rudimentary understanding of the relevant tumour antigens. Nonetheless, practical therapeutic value has been reported in some clinical trials employing vaccines prepared from autologous tumour cells or tumour-associated antigens[131-135]. More recently, efforts to boost anti-cancer immunity have turned to altering the genetic composition of immune cells or cancer cells[136].

THE FUTURE OF VACCINE THERAPY IN THE AGE OF MOLECULAR BIOLOGY

One important reason that we could evoke a boosted immune response in already infected patients was that we administered relatively large doses of a highly purified viral antigen. For HIV this was feasible only through availability of molecularly cloned and expressed antigens, a technology extant for little more than a decade. Antigenic processing and presentation of lymphocytes *in vivo* in our patients may have been enhanced by using an antigen that was expressed in arthropod cells, cells that have somewhat different post-translational modification of proteins compared with mammalian cells. Perhaps equally important, we were able to measure immune responses through use of specific reagents that corresponded to selected antigenic regions or epitopes of interest. Again, this was possible only because we developed and utilized reagents produced in quantity through molecular biological techniques.

It seems likely that materials developed through modern molecular technologies will permit a variety of new approaches to vaccine therapy for many chronic infections. Certainly, specific antigens in conventional adjuvants can be administered, as we demonstrated in our study, but this was a first, simple step toward realizing the full potential of vaccine therapies. Several future strategies can be envisioned:

1 Evaluate multiple variant conformations of an antigen of importance, and selectively administer and boost immunity to the most favourable conformation.
2 Co-administer antigens as mixtures with selected recombinant lymphokines or cytokines chosen to facilitate immune responsiveness.
3 Co-administer antigens along with recombinant immune response gene products such as class I or class II MHC proteins, prepared so as to expedite recognition by CD8 or CD4 surface-positive cells
4 Alternatively, the genes for the proteins above could be delivered into patient cells for expression *in vivo*, so that the antigens, cytokines and other immune response gene products are expressed, processed and presented to the immune system in optimal natural associations.

Vaccine therapy should be considered as an ideal method to probe and analyse the human immune response *in vivo*, so as to devise ever more effective therapies. In 1865 Claude Bernard exhorted that[137]:

> Medicine should be an experimental science ... it should delve into the interior of organisms and find ways of altering, and, to a certain extent, regulating the hidden springs of living machines.

The future holds real promise that, through vaccine therapy, it will be possible to 'regulate the hidden springs' of the immune system in chronic infectious disease such as HIV; perhaps the dreams of our 'immunizator' forebears Auzias-Turenne, Koch and Wright will be realized

CONCLUSION

Vaccine therapy, or active specific immunization with microbe-derived antigens, has been an intellectually appealing strategy for over a century. The giants of microbiology, including Pasteur, Koch and Wright, all shared the belief that the host immune response is accessible to physician-directed manipulation during chronic infection. Other more recent studies have generated highly suggestive evidence in support of this belief, but thus far the efficacy of vaccine therapy remains an unproven assumption. The quest has not been entirely futile; many of the cornerstones of modern microbiology such as delayed-type hypersensitivity, opsonization and antibiotics were discovered during vaccine therapy research studies.

It is to be hoped that vaccine therapy clinical trials will promptly lead to effective new treatments for HIV. Fresh conceptual advances in understanding of HIV immunopathogenesis are likely to ensue from this interventive scientific strategy.

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